REMARKS

Rejections Under 35 U.S.C. 112, second paragraph

Claims 17, 28, 32, and 33 – The Office Action rejects claims 17, 28, 32, and 33 because it is allegedly unclear where the linkage of the peptide to the cobalamin residue occurs. However, the specification states in the final paragraph of page 8 that:

> As used herein, a "residue of a compound of formula I" is a radical of a compound of formula I having one or more open valences. Any synthetically feasible atom or atoms of the compound of formula I may be removed to provide the open valence, provided bioactivity is substantially retained. Based on the linkage that is desired, one skilled in the art can select suitably functionalized starting materials that can be derived from a compound of formula I using procedures that are known in the art. For example, suitable atoms that may be removed include the NH_2 group of the a-carboxamide (illustrated in figure 1) or a hydrogen atom from the NH_2 group of the a-carboxamide, the NH_2 group of the b-carboxamide (illustrated in figure 1) or a hydrogen atom from the NH_2 group of the b-carboxamide, the NH_2 group of the d-carboxamide (illustrated in figure 1) or a hydrogen atom from the NH_2 group of the d-carboxamide, the NH_2 group of the e-carboxamide (illustrated in figure 1) or a hydrogen atom from the NH_2 group of the e-carboxamide, and X at the 6-position (illustrated in figure 1). In addition, the hydrogen atom of the hydroxy group at the 3' position of the sugar, the hydrogen atom from the hydroxyl group at the 3' position of the sugar, the hydrogen atom of the CH_2OH group at the 5' position, or the hydrogen atom from the hydroxyl group at the 5' position of the sugar ring may be removed.

This discussion identifies numerous points of attachment for the peptide linker, and provides more than ample guidance to a skilled worker concerning what a point of attachment is that would be covered by the claims. Because a skilled worker would recognize the metes and bounds of these claims, especially in view of the foregoing specification text, Applicants submit that the claims satisfy the second paragraph of 35 U.S.C. 112.

Claims 17 (line 3), 28 (line 3), and 32 (line 4) – The Office Action rejects claims 17, 28, and 32 because the term "suitable carboxy protecting group" is allegedly unclear. However, the specification states in the definition of amino acid on page 9 that:

> The term also comprises natural and unnatural amino acids bearing amino protecting groups (e.g. acetyl, acyl, trifluoroacetyl, or benzyloxycarbonyl), as well as natural and unnatural amino acids protected at carboxy with protecting groups

(e.g. as a (C_1-C_6)alkyl, phenyl or benzyl ester or amide). Other suitable amino and carboxy protecting groups are known to those skilled in the art (See for example, T.W. Greene, Protecting Groups In Organic Synthesis; Wiley: New York, 1981; D. Voet, Biochemistry, Wiley: New York, 1990; L. Stryer, Biochemistry, (3rd Ed.), W.H. Freeman and Co.: New York, 1975; J. March, Advanced Organic Chemistry, Reactions, Mechanisms and Structure, (2nd Ed.), McGraw Hill: New York, 1977; F. Carey and R. Sundberg, Advanced Organic Chemistry, Part B: Reactions and Synthesis, (2nd Ed.), Plenum: New York, 1977; and references cited therein).

Thus, the specification lists several examples of commonly used protecting groups (e.g. C_{1-6} alkyl, phenyl, or benzyl ester or amide), and also lists several references that discuss in greater detail what is meant by a carboxy protecting group. In light of these disclosures a skilled worker would understand the meaning of carboxy protecting group, and would appreciate the metes and bounds of the rejected claims.

Claims 1-69 – The Office Action rejects claims 1-69 because of various alleged deficiencies in the structure of Figure 1. In reply, Applicants submit herewith a replacement Figure 1. The structure provided in Figure 1 corresponds precisely with the accepted structure of vitamin B12, as discussed in the second paragraph of the background of the specification.

Claims 1-69 – The Office Action rejects claims 1-69 because the structure of Figure 1 is not incorporated into the claims, and variables associated with the structure are not defined in the claims. In reply, Applicants have incorporated figure 1 into all of the independent claims and have defined the constituent variables.

Claim 33, line 3 – The Office Action rejects claim 33 because it is not clear what position R_j is attached to on the phenyl ring. Applicants have cancelled claim 33 from the pending claims.

Claims 55-69 – The Office Action rejects claims 55-69 because of the presence of multiple dependent claims that depend from other multiple dependent claims. Because Applicant cannot discern any multiple dependent claims that depend from other multiple dependent claims, Applicants respectfully request clarification of this rejection.

Claims 64-69 – The Office Action rejects claims 64-69 because the claims are written in "use" format instead of "method" format. In reply, Applicants have cancelled these claims.

Double Patenting

The Office Action rejects various claims under the judicially created doctrine of obviousness-type double patenting based upon Applicants earlier patents numbered 6,211,355, 6,096,290, 5,739,313, and 6,004,533. Applicants respectfully traverse the rejections because the subject matter claimed herein is not obvious over the subject matter of the claims in the prior patents. In particular, the use of a peptide or amino acid linker in a vitamin B12 delivery system is not obvious from the claimed subject matter of the prior patents.

The claims of Applicants' prior patents disclose only the following potential linking moieties for linking the vitamin B12 to the active agent:

$H_2N(CH_2)_{2\text{-}6}NH_2$;

$HO(CH_2)_{2\text{-}6}OH$;

$HO_2C(CH_2)_{2\text{-}6}CO_2H$;

$H_2N(CH_2)_{2\text{-}6}OH$;

$H_2N(CH_2)_{2\text{-}6}CO_2H$; and

$HO(CH_2)_{2\text{-}6}CO_2H$.

(See US 6,211,355, claim 3). In contrast, claims of the present invention cover compounds in which the active agent is linked to the vitamin B12 through a peptide or amino acid. Because Applicants' prior patents do not disclose or suggest the peptide or amino acid linkers of the present invention, they do not support an obviousness-type double patenting rejection.

The Office Action also rejects the claims for obviousness-type double patenting over Applicants' copending applications 10/027,593, 10/028,857, 09/690,197, 09/690,198, 09/626,213, 09/873,142, and 09/873,164. In reply, Applicants agree to submit a suitable terminal disclaimed disclaiming the terminal part of any patent granted on this application that extends beyond the expiration date of U.S.S.N. 10/027,593, 10/028,857, 09/690,197, 09/690,198, 09/973,142, and 09/873,164. Because U.S.S.N. 09/626,213 contains the identical linker disclosure as U.S. Patent Nos. 6,211,355, 6,096,290, 5,739,313, and 6,004,533, Applicants do not agree to file a terminal disclaimer with respect to U.S.S.N. 09/626,213. Applicants note that in agreeing to file this terminal disclaimer they in no way concede the proprietary of an obviousness-type double patenting rejection against any of the foregoing applications.

101 Rejections

The Office Action rejects claims 64-69 under 35 U.S.C. 101 because these claims are written in use format. In reply, Applicants have cancelled these claims.

102 Rejections

The Office Action rejects claims 28-32 and 56-69 under 35 U.S.C. 102(b) as being anticipated by Collins et al. (WO 97/18231). WO 97/18231 is the PCT publication corresponding to U.S. Patent Nos. 6,211,355, 6,096,290, 5,739,313, and 6,004,533, discussed above, and contains the identical disclosure as the foregoing patents. The publication thus discloses the following potential moieties for linking vitamin B12 to an active agent:

$H_2N(CH_2)_{2\text{-}6}NH_2$;

$HO(CH_2)_{2\text{-}6}OH$;

$HO_2C(CH_2)_{2\text{-}6}CO_2H$;

$H_2N(CH_2)_{2\text{-}6}OH$;

$H_2N(CH_2)_{2\text{-}6}CO_2H$; and

$HO(CH_2)_{2\text{-}6}CO_2H$.

Because the claims of the present application only cover compounds in which an active agent is linked to vitamin B12 through an amino acid or peptide linker, they are not anticipated by the disclosure of this PCT publication.

The Office Action also rejects claims 49-51 and 56 under 35 U.S.C. 102(b) as allegedly being anticipated by Niswender et al. (U.S. Patent No. 3,981,863). The Office Action states that Niswender discloses "(proteins such as polylysine may be covalently bonded with Vitamin B12 (column 3, lines 1-9) and (2) procedures for incorporating" ^{125}I and ^{131}I into the molecule. Applicants have cancelled claims 49-51, without prejudice to the subject matter contained therein, in an effort to more promptly advance the prosecution of this application toward allowance.

103 Rejections

The Office Action rejects claims 1-11 and 47 for allegedly being obvious over Niswender et al. According to the Patent Office, it would have been obvious to link a radionuclide to

vitamin B12 through a peptide residue in view of Niswender because Niswender discloses that a protein can be linked to Vitamin B12 in column 3, lines 1-8.

Applicant submits that the Office Action fails to account for the overall teaching of Niswender. Niswender discloses two potential modifications of vitamin B12. In a first modification, Niswender converts a vitamin B12 hapten into a vitamin B12 antigen that can be injected into a rabbit to obtain polyclonal antibodies to vitamin B12. In particular, the reference discloses in column 2, lines 58-68, that a protein can be linked to a vitamin B12 carboxylic to develop the antigen. These antibodies can then be used to assay for vitamin B12. It would serve no purpose to label these particular vitamin B12/protein antigens with a radionuclide. Therefore, this disclosure does not support a prima facie case of obviousness.

In a second modification, Niswender attaches a radioactive iodine to vitamin B12. Niswender prepares this iodinated derivative of vitamin B12 as a competitive binding molecule for a vitamin B12 assay. Niswender uses the compounds of formula (I) and (II) (disclosed in column 1) as "linkers" to attach the iodine to vitamin B12. Niswender discloses that the non-metallic detectable agents can be linked to the compounds of formula (I) and (II) by halogenating the phenolic group contained in the compound of formula (I) or (II). (Column 1, lines 62-65). Niswender only discloses the linkage of non-metallic radionuclides to vitamin B12. Niswender does not disclose the linkage of radionuclides to vitamin B12, a method of linking metallic radionuclides to vitamin B12, or the linkage of metallic radionuclides through a chelating group as required by the present claims. Therefore, Niswender does not support a prima facie case of obviousness against the present claims.

The Office Action rejects claim 49 for allegedly being obvious over Bernstein et al. As noted above, claim 49 has been cancelled without prejudice.

The Office Action rejects claims 1-11, 16, 20, 21, 24, and 47-56 for allegedly being obvious over WO 97/14711. WO 97/14711 discloses the redirection of vitamin B12 receptors on the surface of cells after the receptor/vitamin B12 complex has been internalized by the cell. As explained on page 9, lines 20-25 of the specification, a rerouting moiety is coupled to the vitamin B12 so that when the vitamin B12 is internalized, the rerouting moiety prevents "the receptor from recycling to the surface." The Office Action argues that WO 97/14711 renders the claimed invention obvious because (1) the reference discloses the attachment of a radionuclide to the

rerouting moiety to assess the cellular uptake of the vitamin B12/rerouting moiety conjugate, (2) the reference discloses that rerouting peptides may be covalently attached the vitamin B12, and (3) the reference discloses that vitamin B12 may be conjugated to a radioisotope and used for radiodiagnostic or radiotherapeutic purposes.

The Office Action fails to state a prima facie case of obviousness because the reference would not have motivated a skilled worker to link a radionuclide to vitamin B12 through an amino acid or peptide linker. Even though the publication makes a passing reference to the fact that vitamin B12 can be detectably labeled, the reference says nothing about how the detectable label would be attached to the vitamin B12. Indeed, on pages 13-17 the reference provides an exhaustive listing of linkers that presumably can be used in the invention, and conspicuously omits naming any amino acids or peptides. The bare fact that the reference teaches that peptides can be linked to vitamin B12, combined with the bare fact that the reference teaches that vitamin B12 can be detectably labeled, simply would not have motivated a skilled worker to attach a detectable label to vitamin B12 through a peptide linker. In view of these deficiencies, Applicants respectfully submit that the reference fails to support a prima facie case of obviousness.

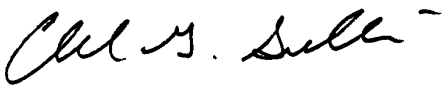
Specification

As requested in the Office Action, enclosed are replacement pages 2-20, 22, 24, 25, and 27-35 of the present specification.

CONCLUSION

Applicants thank the Examiner for the attention he has thus far given to this application, and requests that he contact the undersigned or Sherry Knowles at 404-572-4600 should he have any questions concerning this application.

Respectfully submitted,



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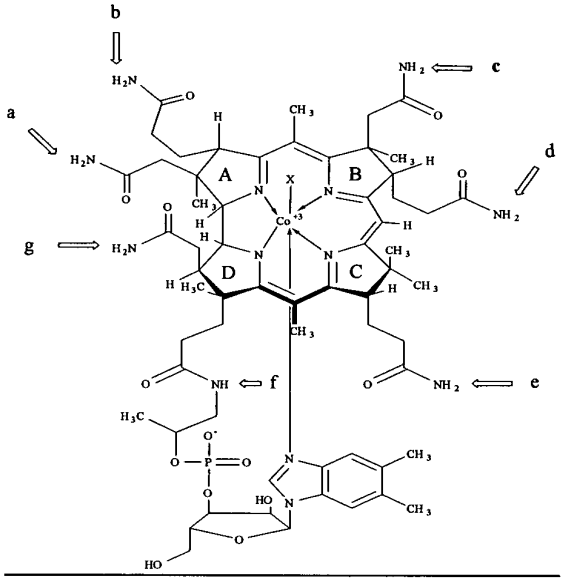
3055872 v1

VERSION OF CLAIMS TO SHOW CHANGES MADE

1) (Once Amended) A compound wherein a residue of a compound of formula I



(I)

is linked to one or more peptide residues or amino acid residues wherein: **X is CN, OH, CH_3 or adenosyl, and [1)]** at least one of the peptide residues or the amino acid residues is linked to one or more chelating groups comprising one or more metallic radionuclides; **[or 2) at least one of the peptide residues or the amino acid residues comprises one or more non-metallic radionuclides;]** or a pharmaceutically acceptable salt thereof.

2) UNCHANGED

3) UNCHANGED

4) CANCELLED.

5) UNCHANGED

6) UNCHANGED

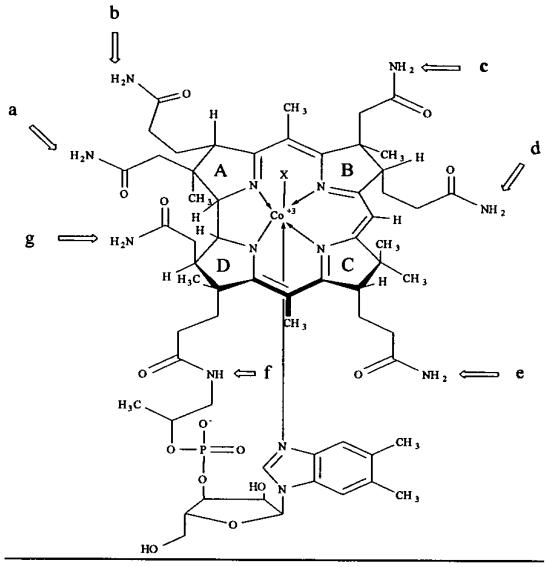
7) UNCHANGED

8) UNCHANGED

9) UNCHANGED

10) UNCHANGED
11) UNCHANGED
12) UNCHANGED
13) UNCHANGED
14) UNCHANGED
15) UNCHANGED
16) UNCHANGED
17) UNCHANGED
18) UNCHANGED
19) UNCHANGED
20) CANCELLED
21) CANCELLED
22) CANCELLED
23) CANCELLED
24) CANCELLED
25) CANCELLED
26) CANCELLED
27) CANCELLED

28) (Once Amended) A compound wherein a residue of a compound of formula I



(I)

is linked to one or more residues of the formula -[NHCH[$(CH_2)_4NH_2$-DET]CO-]$_n$-Q wherein Q is H, (C_1-C_{14})alkyl, or a suitable carboxy protecting group; X is CN, OH, CH_3 or adenosyl; DET is a chelating group residue comprising a metallic radionuclide; and n is between 2 and about 20; or a pharmaceutically acceptable salt thereof.

29) UNCHANGED

30) UNCHANGED

31) UNCHANGED

32) UNCHANGED

33) CANCELLED

34) CANCELLED

35) CANCELLED

36) CANCELLED

37) UNCHANGED

38) UNCHANGED

39) UNCHANGED

40) UNCHANGED

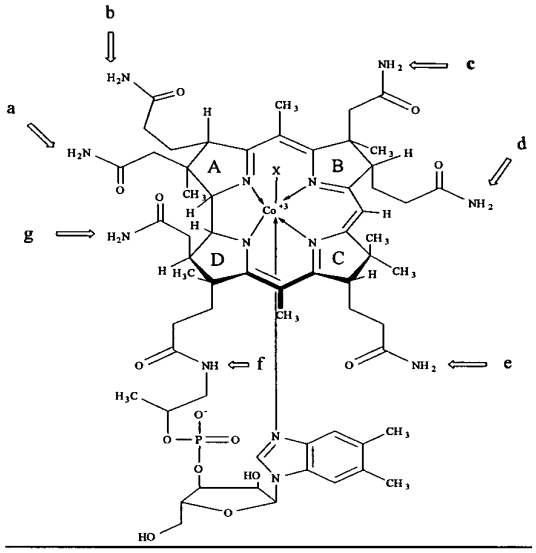
41) UNCHANGED

42) UNCHANGED

43) UNCHANGED

44) UNCHANGED

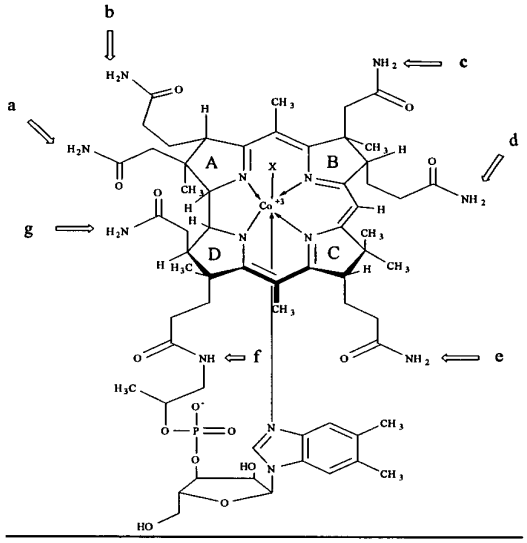
45) (Once Amended) A compound wherein a residue of a compound of formula I



(I)

is linked to a residue of a peptide which is linked to one or more chelating groups comprising a metallic radionuclide; and X is CN, OH, CH_3 or adenosyl; or a pharmaceutically acceptable salt thereof.

46) (Once Amended) A compound wherein a residue of a compound of formula I



(I)

is linked to a residue of an amino acid which is linked to one or more chelating groups comprising a metallic radionuclide; and X is CN, OH, CH_3 or adenosyl; or a pharmaceutically acceptable salt thereof.

47) CANCELLED

48) CANCELLED

49) CANCELLED

50) CANCELLED

51) CANCELLED

52) CANCELLED

53) CANCELLED

54) CANCELLED

55) CANCELLED

56) A pharmaceutical composition comprising a compound of any one of claims **[1-55]** **1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 28, 29, 30, 31, 32, 37, 38, 39, 40, 41, 42, 43, 44, 45, or 45** and a pharmaceutically acceptable carrier.

57) A method for imaging a tumor in mammalian tissue comprising administering to the mammal an amount of a compound of any one of claims **[1-55]** **1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 28, 29, 30, 31, 32, 37, 38, 39, 40, 41, 42, 43, 44, 45, or 45**; and detecting said compound.

58) The method of claim 57 wherein the mammal is a human.

59) The method of claim 57 wherein the mammalian tissue is located in the breast, lung, thyroid, lymph node, genitourinary system, musculoskeletal system, gastrointestinal tract, central or peripheral nervous system, head, neck, or heart.

60) A method for treating a tumor in a mammal comprising administering to the mammal an effective therapeutic amount of a compound of any one of claims **[1-55]** **1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 28, 29, 30, 31, 32, 37, 38, 39, 40, 41, 42, 43, 44, 45, or 45**; wherein said compound comprises at lease one therapeutic radionuclide.

61) The method of claim 60 wherein the mammal is a human.

62) The method of claim 60 wherein the mammalian tissue is located in the breast, lung, thyroid, lymph node, genitourinary system, musculoskeletal system, gastrointestinal tract, central or peripheral nervous system, head, neck, or heart.

63) A compound of any one of claims **[1-55]** **1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 28, 29, 30, 31, 32, 37, 38, 39, 40, 41, 42, 43, 44, 45, or 45** for use in medical therapy or diagnosis.

64) CANCELLED

65) CANCELLED

66) CANCELLED

67) CANCELLED

68) CANCELLED

69) CANCELLED